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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/691,763	10/18/00	VERTINO	P E0355/7003/E

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EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1655	16

DATE MAILED: 09/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/691,763	Applicant(s) VERTINO, PAULA M.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,47 and 110-122* is/are pending in the application.

4a) Of the above claim(s) *5,13,21,30,38,58,61,67,68,71,72,89,95,101 and 105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,47 and 110-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (Claims 1, 47) in Paper No. 15 is acknowledged.

Priority

2. This application claims priority to provisional application 60/159,975, October 18, 1999.

Information Disclosure Statement

3. Several entries from the IDS filed April 12, 2001 are objected to because the references do not provide the date. The MPEP requires, "Each publication shall be identified by author (if any), title, relevant pages of the publication, date and place of publication." The Genbank Entries do not contain a date. One suggested format includes: Database (Name and organization), Actual Owner or source of database, accession number, date. Thus, cite numbers C5-C11 are objected to and have not been considered. Applicant is invited to submit these references and the references will be considered without need for a fee or petition.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 47, 110-122 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 110-113 are broadly drawn to a method for identifying a subject at risk for developing a tumor characterized by abnormal methylation of a CpG island contained TMS1 nucleic acid by determining the level of methylation of a CpG island in a biological sample, and comparing the level of methylation to a control wherein an increase in the level of methylation identifies a subject at risk of developing the tumor.

Claims 47, 114-122 are broadly drawn to a method for identifying a subject having cancer who is at risk of being non-responsive to an anti-cancer therapy by determining the level of methylation of a CpG island in a biological sample, and comparing the level of methylation to a control wherein an increase in the level of methylation identifies a subject at risk of being non-responsive to an anti-cancer therapy.

The specification provides analysis of cell lines and breast tumors. As seen in Figure 4, 12 of the 18 tumors examined are illustrated (pg. 13 of specification). Of the 12 breast tissues and paired tumors, no normal tissues were methylated when the tumor was unmethylated. This suggests that if methylation is compared in the tissues, a presence of methylation is suggestive of tumor tissue.

The art supports that methylation of CpG islands is often indicative of cancers. As provided in Nelson et al (US Pat. 5,552,277, September 1996) prostate cancer may

be detected by detecting hypermethylation in the promoter of GSTP1 DNA. Further, Baylin et al. (US Pat. 5,756,668, May 1998) teaches HIC-1 is hypermethylated in cancer. Finally, Herman et al (US Pat. 5,786,146, July 1998) teaches detection methods for detecting methylation.

However, neither the specification nor the art teaches how to make and use the invention as broadly as claimed. First, it is unclear whether the other 6 tumors not illustrated are consistent with the findings of the tumors or whether methylation was seen normal tissues but absent in the tumors. The specification teaches that only 12 of the 18 tumors examined are illustrated. It is unclear what the results of these tests are since applicant has not described the results in any way.

Secondly, the specification teaches analyzing several cell lines. However, increased of SEQ ID NO: 4 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this would necessarily be hypermethylated in primary tumor tissue as compared to non-tumor tissue. Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." As discussed by Dermer *et al.* the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low. Thus, the studies with cell lines, while interesting provide little insight into tumors without undue experimentation.

Thirdly, the claims are broadly drawn to any tumor and cancer. The specification has only provided results directed to breast tumors (Figure 4). The identification of a CpG island indicative of breast tumors does not provide guidance to any cancer. There is no suggestion that lung, prostate, skin or any other tumors would have any predictive value from the hypermethylation of TMS1 at SEQ ID NO: 4. Further, not all cancers involve tumors, such as leukemia. A suggestion that the hypermethylation of TMS1 CpG island of SEQ ID NO : 4 is indicative of any tumor or cancer is unpredictable. The skilled artisan would be required to perform additional experiments which would be undue. The results of such experiments would further be unpredictable.

Additionally, the specification does not support hypomethylation of TMS1 as indicative of risk for a tumor. The specification only provides hypermethylation of TMS1 as indicative of a breast tumor. The claim broadly reads abnormal methylation which includes both hypermethylation and hypomethylation. It is unpredictable whether hypomethylation has effect on risk of developing a breast tumor, and further any tumor or cancer.

Finally, the specification provides no guidance to determining non-responsiveness to anti-cancer therapy by detecting the hypermethylation. The specification does not appear to have performed any non-responsive studies with respect to methylation. It is unclear which of these patients are non-responsive to treatment. One means for supporting this claim would have been a study which found hypermethylation in patients at SEQ ID NO: 4 and compared the data to data with respect to patient's non-responsiveness to anti-cancer therapy. It is unpredictable

whether any or all of these individuals by merely having hypermethylation are non-responsive to anti-cancer therapy. The skilled artisan would be required to perform additional analysis to determine whether the hypermethylation has any effect on responsiveness to a drug. Further, as provided in Claim 122, it is unclear why a subject at risk for being non-responsive to an anti-cancer therapy would be administered such a therapy.

Conclusion

5. No claims allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
September 17, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600